REMARKS

Claims 1 to 13, 20, 22, and 24 are pending in the application. Claim 22 stands withdrawn and claims 14 to 19, 21, and 23 were previously canceled. Claim 1 has been amended to correct an obvious typographical error and to recite the subject matter with even greater particularity. Claim 2 has been amended to correct antecedent basis and informalities. New claim 24 has been added. Support for the amendments can be found throughout the specification as originally filed, *e.g.*, page 1, line 11; page 4, lines 29 and 33; and page 8, line 5. The amendments add no new matter to the application.

Withdrawn Rejections

Applicant notes with appreciation that all prior rejections have been withdrawn. The claims are now rejected, however, on the basis of new anticipation and obviousness rejections. In view of the amendments and the remarks that follow, the Office is asked to reconsider and withdraw the present rejections.

Rejections under 35 U.S.C. § 102(a) and (b)

1. Claims 1-3, 6-9, 13, and 20 were rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Ribeiro *et al.* (*Lancet* 360:461-462; "Ribeiro"). The Office alleges that Ribeiro teaches "a method of predicting whether a patient has cardiomyopathy comprising analyzing the BNP levels of Chagas' disease patients" (Office Action at page 4).

Applicant respectfully traverses and submits that claim 1, even prior to the present amendment, is novel over Ribeiro. Ribeiro recites that "[p]atients with Chagas' disease have high plasma concentrations of BNP in association with impaired left ventricular function" (*see* page 462, col. 1, lines 16-18). Applicant sees no reference in Ribeiro to cardiomyopathy or myocarditis, so surmises that the Office's position is that left ventricular dysfunction (LVD) is equivalent to cardiomyopathy or myocarditis. However, a skilled practitioner would appreciate that LVD is wholly distinct from cardiomyopathy and myocarditis. LVD, with subsequent congestive heart failure, constitutes the final stage for a host of cardiac disorders, including

cardiomyopathy and myocarditis. A patient having LVD does not necessarily suffer from cardiomyopathy or myocarditis. Ribeiro does not describe cardiomyopathy or myocarditis, or associate an elevated BNP level in Chagas disease with cardiomyopathy or myocarditis and therefore, does not anticipate the present claims.

Further, skilled practitioners would appreciate that Chagas disease does not necessarily involve the myocardium. Ribeiro admits as much in saying that "[n]one of the patients with Chagas' disease with a normal electrocardiogram and chest radiograph had LVEF of 0·40 or less" (*see* page 462, col. 1, lines 10-12; emphasis added). One of skill in the art would reasonably conclude that a high level of BNP in Ribeiro's study indicates only that the patient has LVD, which may or may not be related to Chagas disease. For example, a practitioner would understand that the patient may have LVD and a high BNP level because of a valvular disease of another etiology. In contrast, applicant has demonstrated that a high level of BNP indicates that cardiomyopathy, myocarditis, or both cardiomyopathy and myocarditis will arise as a result of an infection in a patient. Accordingly, Ribeiro does not anticipate claims 1-3, 6-9, 13, and 20 and applicant respectfully requests that the rejection be reconsidered and withdrawn.

2. Claims 1-3, 8, 13, and 20 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Arad *et al.* (*Cardiology* 87:12-17; "Arad"). The Office alleges that Arad teaches a method of predicting whether a patient has cardiomyopathy by analyzing the BNP levels in one patient of the study and that abnormal BNP levels are a useful marker of heart dysfunction (Office Action at pages 6 and 7).

Applicant disagrees. As noted at page 2, line 29, to page 3, line 3 of the originally filed specification, BNP levels have been shown to be elevated in specific cardiomyopathies, but the literature at the time of the present invention did not disclose that BNP and ANF levels are elevated in inflammatory cardiomyopathies that arise as a result of an infection. Arad studied heart function and heart failure (a mechanical concept) and does not even mention an infection of any kind. Arad states that "[i]n the current study we evaluated the hormone levels in patients with ischemic heart disease manifested predominantly by angina pectoris with or without overt

heart failure" (*see* page 16, col. 2, lines 3-6; emphasis added). In contrast, the present claims recite methods of predicting whether cardiomyopathy, myocarditis, or both, will arise as a result of an infection in a human patient. As shown by applicant, elevated levels of BNP or BNP and ANF are measured after a patient suffers an infection and these levels correlate with the occurrence of cardiomyopathy and/or myocarditis. Arad does not disclose that one should assess BNP, or BNP and ANF, in order to predict whether cardiomyopathy or myocarditis will arise as a result of an infection. Accordingly, Arad does not anticipate claims 1-3, 8, 13, and 20, and applicant respectfully requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

1. Claims 1-4, 8, 11-13, and 20 were rejected as allegedly obvious over Arad and Totsune *et al.* (*Regul Pept* 63:141-147; "Totsune"). In support of this rejection, the Office refers to the disclosure of Arad as it applies to claims 1-3, 8, 13, and 20. With respect to claims 11 and 12, the Office asserts that "it would be obvious to perform multiple tests on multiple samples collected at different times because the Scientific method teach [*sic*] that experiments should be reproducible. Additionally, testing BNP and ANP levels may give an indication as to how to predict the progress of the cardiomyopathy" (Office Action at page 9). In addition, the Office asserts that it would be obvious to substitute the body fluid sample taught in Arad, *i.e.* plasma, for the body fluid sample taught in Totsune, *i.e.* urine. Applicant traverses.

The distinguishing features of claim 1 over Arad are discussed in detail above. Totsune does not cure the deficiencies of Arad. Totsune is combined with Arad by the Office in an attempt to provide the element recited in claim 4, *i.e.*, urine as the body fluid. Totsune does not remedy the other shortcomings of Arad. In particular, Totsune does not teach that an increased BNP level is a useful marker of infection-related cardiomyopathy or myocarditis. Regardless of whether or not multiple tests can be performed on multiple samples collected at different times, or whether ANF can be detected in the urine, the present methods are non-obvious because, *inter alia*, nothing in the combined teachings of Arad and Totsune suggest that BNP, or BNP and ANF, can be used as predictive indicators of cardiomyopathy or myocarditis in human patients

who have an infection. What must be obvious is the claimed invention as a whole. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious" (MPEP at 2141.02, emphasis in original, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). Thus, the determination is not whether it would have been obvious to perform multiple tests on multiple samples collected at different times, but whether it would have been obvious to do so as a predictive indicator for cardiomyopathies and myocarditis that arise as a result of an infection. Similarly, the determination is not whether it would have been obvious to analyze urine, but whether it would have been obvious to analyze BNP, or BNP and ANF, in urine as a predictive indicator as required by the claims.

Applicant submits that skilled practitioners would not be able to arrive at the subject matter of claim 1. As claim 1 is non-obvious, all of its dependents, including claims 2-4, 8, 11-13, and 20 are also non-obvious for at least the same reasons. Accordingly, applicant requests that the rejection be withdrawn.

2. Claims 1-3, 5, 8, 11-13, and 20 were rejected as allegedly obvious over Arad and Kaneko *et al.* (*Brain Res* 612:104-109 (Abstract only); "Kaneko"). In support of this rejection, the Office refers to the disclosure of Arad as it applies to claims 1-3, 8, 13, and 20. Regarding claims 11 and 12, the Office asserts that "it would be obvious to perform multiple tests on multiple samples collected at different times because the Scientific method teach [*sic*] that experiments should be reproducible. Additionally, testing BNP and ANP levels may give an indication as to how to predict the progress of the cardiomyopathy" (Office Action at page 13). In addition, the Office asserts that it would be obvious to substitute the body fluid sample taught in Arad, *i.e.* plasma, for the body fluid sample taught in Kaneko, *i.e.* cerebrospinal fluid. Applicant respectfully disagrees.

The distinguishing features of claim 1 over Arad are discussed in detail above. Kaneko does not cure the deficiencies of Arad. Kaneko is combined with Arad by the Office in an

attempt to provide the element recited in claim 5, *i.e.*, cerebrospinal fluid as the body fluid. Kaneko does not remedy the other shortcomings of Arad. In particular, Kaneko does not teach that an increased BNP level is a useful marker of infection-related cardiomyopathy or myocarditis. Regardless of whether or not multiple tests can be performed on multiple samples collected at different times, or whether BNP and ANF can be detected in cerebrospinal fluid, the present methods are non-obvious because, *inter alia*, nothing in the combined teachings of Arad and Kaneko suggest that BNP, or BNP and ANF, can be used as predictive indicators of cardiomyopathy or myocarditis in human patients who have an infection. What must be obvious is the claimed invention as a whole. "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious" (MPEP at 2141.02, emphasis in original, citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983)). Thus, the determination is not whether it would have been obvious to perform multiple tests on multiple samples collected at different times, but whether it would have been obvious to do so as a predictive indicator for cardiomyopathies and myocarditis that arise as a result of an infection. Similarly, the determination is not whether it would have been obvious to analyze cerebrospinal fluid, but whether it would have been obvious to analyze BNP, or BNP and ANF, in cerebrospinal fluid as a predictive indicator as required by the claims. As claim 1 is non-obvious, all of its dependents, including claims 2, 3, 5, 8, 11-13, and 20 are also non-obvious for at least the same reasons. Accordingly, the rejection should be withdrawn.

3. Claims 1-3, 6-9, 11-13, and 20 were rejected as allegedly unpatentable over Arad in view of Scaglione *et al.* (*J Parasitol* 87:923-926). The Office refers to the disclosure of Arad as it applies to claims 1-3, 8, 13, and 20. The Office further asserts that claims 6 to 9 are rendered obvious by the combination of Arad and Scaglione. In particular, the Office asserts that the following elements not found in Arad are allegedly described by Scaglione: "the infection comprises a viral infection, a rickettsial infection, a bacterial infection, a mycobacterial infection, a spirochetal infection, a fungal infection, or a parasitic infection (claim 6); "the parasitic

infection comprises *Trypanosoma cruzi*" (claim 7); "the at least one antibody comprises a polyclonal antibody, a monoclonal antibody, or a combination thereof" (claim 8); and "the at least one antibody comprises a polyclonal antibody" (claim 9). Applicant respectfully traverses.

The distinguishing features of claim 1 over Arad are discussed in detail above. Scaglione does not cure the deficiencies of Arad. Scaglione is combined with Arad by the Office in an attempt to arrive at claims 6 to 9. As discussed in applicant's previous Reply filed June 1, 2009, Scaglione does not teach a method of determining BNP, nor does Scaglione teach that levels of BNP are elevated in cardiomyopathy and myocarditis that arise as a result of an infection. Thus, it would not have been obvious to determine the level of BNP or both BNP and ANF in a patient to detect whether there is myocardial involvement following an infection. The present methods are non-obvious because nothing in the combined teachings of Arad and Scaglione suggest that BNP, or BNP and ANF, can be used as predictive indicators of cardiomyopathy or myocarditis in human patients who have an infection.

Moreover, as discussed in applicant's previous Reply, Scaglione was published one year earlier and authored by four of the same researchers as the previously cited Puyo *et al.* reference (*Regulatory Peptides* 105:139-143; "Puyo"). The authors in the later reference of Puyo examined human patients and found no predictive role for ANF. Puyo teaches away from the present methods by reporting that "plasma ANF does not seem to be a prognostic marker of future development of chagasic heart disease in asymptomatic patients" (Puyo at pages 142-143). Like Scaglione, Puyo is silent regarding BNP. Thus, viewing these three references together, skilled practitioners would have no reason to believe that BNP or ANF could be used as indicators that cardiomyopathy, myocarditis, or both cardiomyopathy and myocarditis, will arise as a result of an infection in a human patient. Therefore, skilled practitioners would not have arrived at the presently claimed methods no matter how Arad and Scaglione are combined. As claim 1 is non-obvious, all of its dependents, including claims 2, 3, 6-9, 11-13, and 20 are also non-obvious for at least the same reasons. Accordingly, the rejection should be withdrawn.

4. Claim 10 was rejected as allegedly unpatentable over Arad in view of Scaglione and further in view of Mischak *et al.* (WO 97/32900; "Mischak"). The Office refers to the disclosures of Arad and Scaglione as they apply to claims 1-3, 6-9, 11-13, and 20 and concedes that Arad and Scaglione do not teach the element of "the at least one antibody comprises a monoclonal antibody" (Office Action at pages 18 and 19). Mischak is combined with Arad and Scaglione by the Office in an attempt to arrive at claim 10. Applicant respectfully traverses.

The distinguishing features of claim 1 over Arad and Scaglione are discussed in detail above. Mischak does not cure the deficiencies of Arad and Scaglione. In particular, Mischak does not teach that an increased BNP level is a useful marker of infection-related cardiomyopathy or myocarditis. Mischak describes only reagents and assays for the quantification of human BNP in plasma and serum, including monoclonal antibodies. Mischak does not teach or suggest that an increase in the level of BNP, or both BNP and ANF in a sample from a patient, compared to the level of BNP, or both BNP and ANF in a control group, indicates that cardiomyopathy, myocarditis, or both cardiomyopathy and myocarditis will arise as a result of an infection in the patient. Mischak fails to overcome the deficiencies of Arad and Scaglione, and therefore does not render obvious claim 10. Accordingly, applicant respectfully requests the rejection be reconsidered and withdrawn.

Applicant respectfully submits that the Office has not established a *prima facie* case of obviousness against the presently claimed methods. No combination of Arad, Totsune, Kaneko, Scaglione, and Mischak, teach or suggest every element of the claims. Further, skilled practitioners would not have been motivated by these references, or anything else in the art, to modify the method described in Arad in an attempt to arrive at applicant's claimed methods. Even if a skilled practitioner were to combine these references, the claimed methods still would not have been obtained because they do not teach or suggest all recited elements. Applicant therefore respectfully requests that these rejections be reconsidered and withdrawn.

CONCLUSION

Applicant submits that the pending claims are allowable and request early and favorable action thereon. Applicant does not concede any positions of the Office that are not expressed above, nor does applicant concede that there are not other good reasons for patentability of the presented claims or other claims.

The Petition for Three-Month Extension of Time fee ($1110) is being paid on the electronic filing system by way of deposit account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14703-0002001.

Respectfully submitted,

Date: 2/22/10

/Todd E. Garcia, Reg. No. 54,112/
Todd E. Garcia, Ph.D.
Reg. No. 54,112

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

22253443.doc